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MECHANISMS OF IMPAIRED ALVEOLAR FLUID CLEARANCE

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Abstract

Impaired alveolar fluid clearance (AFC) is an important cause of alveolar edema fluid accumulation in patients with acute respiratory distress syndrome (ARDS). Alveolar edema leads to insufficient gas exchange and worse clinical outcomes. Thus, it is important to understand the pathophysiology of impaired AFC in order to develop new therapies for ARDS. Over the last few decades, multiple experimental studies have been done to understand the molecular, cellular, and physiological mechanisms that regulate AFC in the normal and the injured lung. This review provides a review of AFC in the normal lung, focuses on the mechanisms of impaired AFC, and then outlines the regulation of AFC. Finally, we summarize ongoing challenges and possible future research that may offer promising therapies for ARDS.

Keywords

acute lung injury; acute respiratory distress syndrome; alveolar fluid clearance

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of non-cardiogenic pulmonary edema caused by the consequence of an increase in lung epithelial and endothelial permeability (Ranieri et al., 2012; Matthay et al., 2019b). ARDS is an important cause of morbidity and mortality in critically ill patients, including recent COVID-19 pneumonia (Bellani et al., 2016; Hasan et al., 2020). Although lung protective ventilation strategies have largely reduced mortality of patients with ARDS (Amato et al., 1998), it is still necessary to develop novel therapies to further reduce mortality. A hallmark of ARDS is the accumulation of protein-rich edema fluid in the alveolar component of the lung caused by increased permeability to liquid, protein, neutrophils, and red blood cells into the airspaces, which leads to impaired gas exchange and respiratory failure (Morty et al., 2007; Huppert and Matthay, 2017; Matthay et al., 2019b).

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Although the reabsorption of pulmonary edema fluid from the alveoli is necessary for the resolution of ARDS, alveolar fluid clearance (AFC) is impaired early in the clinical course of acute respiratory failure in the majority of patients (Ware and Matthay, 2001). Impaired AFC is an important cause of persistent alveolar edema, and preserved AFC is associated with better clinical outcomes (Sznajder, 2001; Ware and Matthay, 2001; Berthiaume and Matthay, 2007; Morty et al., 2007; Matthay, 2014; Huppert and Matthay, 2017). Many clinical and experimental studies have focused on specifying mechanisms for impaired AFC in ARDS models and patients, and how to potentially to enhance AFC, which may hasten the resolution of ARDS and establish therapeutic targets for ARDS.

This article focuses on the mechanisms of impaired AFC. The first section explains the reabsorption of pulmonary edema fluid from the alveoli in the normal lung. The second section considers the pathologic mechanisms that impair the removal of pulmonary edema and the treatments of impaired AFC. The final section briefly considers some of the potential research to the resolution of lung edema for ARDS.

ALVEOLAR FLUID CLEARANCE IN NORMAL LUNG

Alveoli cover a surface that measures more than 100 square feet, 99% of which is composed of alveolar epithelial cells (Colebatch and Ng, 1992). Approximately 90% of the alveolar epithelium surface area is covered with alveolar type I cells, with 10% covered with type II cells (Crapo et al., 1982; Knudsen and Ochs, 2018). In normal lungs, alveolar epithelial cells have several roles; (1) protect lung tissues from virus or bacteria by bounding each other with tight junction, (2) keep the alveoli open by reducing the surface tension, and (3) clear excess alveolar fluid during birth and recovery from pulmonary edema (Matthay et al., 2019b). Since passive movement of even small solutes through alveolar epithelium is highly restricted by the tight epithelium in the normal lungs, the mechanisms responsible for the regulation of pulmonary edema fluid across the alveolar epithelium were poorly elucidated until studies in the 1980s. Studies in sheep offered the first evidence that pulmonary edema fluid clearance is dependent on active ion transport, where clearance of small molecules and water occurred against an increase protein concentration in the alveolar fluid (Matthay et al., 1982). It is now commonly recognized that active ion transport by sodium channel in alveolar epithelial cells is the primary force for AFC (Matthay et al., 2002).

Alveolar epithelial cells have polarity; sodium enters the apical cell surface through sodium channels while basolaterally localized Na/K-ATPase establishes a transepithelial sodium concentration gradient by extruding sodium out of epithelial cells (Matthay, 2014). This sodium concentration gradient provides the force to drive fluid from the airspaces into the lung interstitium, where it is cleared by the lymphatic drainage or vasculature into circulation (Bhattacharya et al., 1984). In addition to sodium channels, cystic fibrosis transmembrane conductance regulator (CFTR: a chloride channel), aquaporin (AQP: a water channel) are also involved in AFC. Although alveolar epithelial type II cells were initially thought to be the main cell responsible for AFC, studies in the *in situ* lungs demonstrated that alveolar epithelial type I cells express sodium channels and CFTR on the apical surface and Na/K-ATPase on the basolateral surface, supporting the important role for type I cells in AFC (Borok et al., 2002; Johnson et al., 2002; Johnson et al., 2006). In normal lung, the

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speed determining factor for the resolution of pulmonary edema is the reabsorption of edema fluid across alveolar epithelial barrier. Figure 1 summarizes the pathways and principal transporters responsible for the resolution of alveolar edema in the normal lung.

Epithelial sodium channel

Epithelial sodium channel (ENaC), also known as amiloride sensitive sodium channel is a membrane bound ion channel that selectively absorb sodium into the epithelial cell. ENaC contains of three subunits (α, β, γ) and was found to be expressed throughout the lung epithelium as well as kidneys, large intestine, sweat glands, and other organs (Canessa et al., 1994). Amiloride, a specific antagonist for ENaC inhibited approximately 70% of basal fluid clearance in experimental models, and in the human lung (Jayr et al., 1994; Tessier et al., 1996; Nielsen et al., 1998; Lee et al., 2009). ENaC α subunit deficient mice failed to clear lung fluid at birth and died from respiratory distress (Hummler et al., 1996). In contrast, overexpression of ENaC in the mouse lower airways enhanced sodium absorption, and depleted the airway surface fluid (Mall et al., 2004). These findings indicate that ENaC is important for maintaining alveolar fluid homeostasis. Interestingly, a case report described a neonate with loss of function mutation in ENaC α-subunit who did not develop respiratory failure immediately after birth (Huppmann et al., 2011). Therefore, AFC might be less dependent on ENaC in human lungs compared with mice. Some experimental studies also described the role of other sodium channels other than ENaC in maintaining basal fluid clearance, which shows the incomplete inhibition of amiloride on AFC (Feng et al., 1993; Junor et al., 1999; Trac et al., 2017).

Na/K-ATPase

Na/K-ATPase is a plasma membrane ion-transporting enzyme found in all animal cells. Na/K-ATPase maintains electrochemical sodium and potassium gradients across the plasma membrane by pumping sodium out of the cell and potassium into the cell fueled by hydrolysis of ATP (Matthay et al., 2002; Vadász et al., 2007; Lecuona et al., 2009). Na/K-ATPase exists on the basolateral surface and drives behind ENaC-mediated sodium uptake into the epithelial cells. Ouabain, a specific antagonist of the Na/K-ATPase, inhibits AFC in isolated, perfused fluid-filled sheep, rabbit, and mice lungs (Sakuma et al., 1993; Jayr et al., 1994; Icard and Saumon, 1999). Decreased expression of Na/K-ATPase α subunits reduced cyclic-adenosine monophosphate (cAMP) stimulated AFC (Looney et al., 2005). Conversely, alveolar overexpression of the Na/K-ATPase β1-subunit restored active transepithelial sodium transport and AFC in a rat model of acute hydrostatic pulmonary edema (Azzam et al., 2002).

CFTR

Studies for ion transport across alveolar epithelial cells focused on the sodium ion transporters (i.e., ENaC and Na/K-ATPase) for long time. Chloride transport is necessary to maintain electrical neutrality to match cationic sodium clearance from the alveoli. Some experimental studies described that chloride may move through transcellular and paracellular pathways (Ingbar et al., 2009). CFTR is a chloride channel expressed on the apical membrane of alveolar epithelial cells. In the presence of cAMP stimulation such as β-adrenergic agonist, CFTR provides a permissive effect for stimulated AFC (Fang et

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al., 2006). Mice that lack function of CFTR did not increase AFC with exogeneous or endogenous β-adrenergic agonist stimulation (Fang et al., 2002). Glibenclamide, an inhibitor for CFTR, also inhibited cAMP-stimulated chloride transport in mouse and human lungs (Fang et al., 2002). Upregulation of CFTR function mediated by Adenovirus in the lungs of mice and rats significantly increased AFC, an effect that was cancelled by the chloride channel inhibitors (Mutlu et al., 2005). Many experimental studies support the important role of CFTR and chloride transport in cAMP-stimulated AFC from the distal airspaces.

Aquaporins

Aquaporins are water transporting channel proteins expressed in the membrane of epithelial, endothelial, and other cells (Nielsen et al., 1993; Verkman, 2007). The mammalian lung expresses several types of aquaporins; aquaporin-1 was expressed throughout the lung microvascular endothelia, and aquaporin-5 was expressed on the apical surface of alveolar epithelial type I cells (Verkman, 2007). Type I cells have high alveolar water permeability, primarily because of the existence of aquaporin-5 (Dobbs et al., 1998). However, experimental studies using knockout of aquaprin-1 and -5 indicated that the deficiency of aquaporins did not change the speed of AFC (Bai et al., 1999) (Ma et al., 2000). The water clearance driven by the ion transport gradient across the alveolar epithelium might mainly occur through paracellular pathways.

MECHANISMS FOR IMPAIRED ALVEOLAR FLUID CLEARANCE

The majority of patients with ARDS have impaired AFC. Impaired AFC is associated with poor clinical outcomes, including prolonged mechanical ventilation and mortality (Ware and Matthay, 2001). The mechanisms responsible for impaired AFC have been studied in numerous experimental models of lung injury. Multiple conditions explain why AFC is impaired in ARDS (Figure 2).

Infection

Infection is the most common cause for ARDS (Bellani et al., 2016). Infection leads to lung edema by promoting epithelial and endothelial permeability. *Mycoplasma* infection decreased AFC by inhibiting function of ENaC via the production of reactive species (Hickman-Davis et al., 2006). Not only live bacteria, but endotoxin instilled into the distal airspaces caused pulmonary edema with the loss of AFC (Lee et al., 2009). Interestingly, a recent study in the *ex vivo* perfused human lung indicates that bacteremia induced by high doses of intravenous *S. pneumoniae* did not impair AFC nor injure the alveolar epithelium, whereas lungs exposed to airspace *S. pneumoniae* decreased AFC. In addition, the bacteria in the perfusate was cleared in part by the neutrophils and alveolar macrophages through interstitial pathways. These findings identify one mechanism by which the lung and the alveolar epithelium are resistant against injury in bacteremia (Ross et al., 2020). Not only bacteria, but also viral infection impairs AFC. Infection of respiratory epithelial cells with respiratory syncytial virus downregulates ENaC by nucleotide release and up-regulating inducible nitric-oxide synthase (Song et al., 2009). Influenza A virus also has physiologically significant inhibitory effects on AFC, which result from ENaC, Na/K-ATPase, and CFTR dysfunction during the acute infection period (Wolk et al., 2008).

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Dysfunction of CFTR persisted beyond the infection period. Influenza A virus mediated inhibition of AFC could be reversed by β-adrenergic agonists (Brand et al., 2018). Thus, pulmonary infections can impair AFC.

Inflammation

In ARDS patients, inflammatory responses inevitably occur after a variety of insults such as bacteria, viruses, and ventilator-induced lung injury and exacerbate alveolar epithelial injury (Han and Mallampalli, 2015). Pro-inflammatory cytokines are elevated in the blood and broncho-alveolar fluid in patients with ARDS, including TGF-β, TNF-α, IL-1β, IL-6, and IL-8 (Meduri et al., 1995; Budinger et al., 2005). Increased activity of TGF-β, TNF-α, and IL-1β in the distal airspaces during acute lung injury promotes alveolar edema by reducing AFC (Frank et al., 2003a; Dagenais et al., 2004; Roux et al., 2005; Peters et al., 2014). This reduction in AFC is attributable in large part to a reduction in apical membrane ENaC expression. IL-8 inhibits cAMP-stimulated AFC (Roux et al., 2013). One *in vitro* study demonstrated that alveolar edema fluid from patients with acute lung injury reduces net fluid transport across human alveolar epithelial type II cells, inducing a reduction in genes and proteins of ENaC, Na/K-ATPase, and CFTR (Lee et al., 2007). Although neutrophils are primary cells for innate immunity, *in vivo* experiments provide the evidence that neutrophils can prevent the upregulation of AFC by catecholamines due to the oxidant injury to the alveolar epithelium (Modelska et al., 1999). Inflammation also activates coagulation pathways in ARDS (Livingstone et al., 2021). Proteases such as thrombin increased vascular permeability and induce lung edema. In addition, thrombin impairs AFC by promoting endocytosis of Na/K-ATPase (Vadász et al., 2005).

Hypoxia/Hypercapnia

Hypoxia is a main feature of ARDS. Exposure to hypoxia accelerated alveolar permeability and induced pulmonary edema in isolated rat lungs perfused at constant pressure (Dehler et al., 2006). Hypoxia reduced AFC by downregulating expression and activity of epithelial sodium channels including ENaC and Na/K-ATPase on alveolar epithelial cells, in part by triggering endocytosis or ubiquitination through reactive oxygen species (Suzuki et al., 1999; Wodopia et al., 2000; Vivona et al., 2001; Dada et al., 2003; Jain and Sznajder, 2005; Comellas et al., 2006). The depressant effects of hypoxia are reversed rapidly by reoxygenation (Planès et al., 1997). Therefore, the supplemental oxygen administration to patients with acute respiratory failure may in itself improve the reabsorption of alveolar edema. Meanwhile, hyperoxia also impaired AFC and caused significant mortality in experimental study, by decreasing Na/K-ATPase function (Hardiman et al., 2001). These findings help explain the harm of hyperoxia in critically ill patients in multiple clinical trials (Hochberg et al., 2021; Singer et al., 2021). There is also evidence that hypercapnia can impair AFC, independently of extracellular and intracellular pH, by inhibiting Na/K-ATPase function (Briva et al., 2007). Thus, maintaining optimal oxygenation and correction of hypercapnia in patients with ARDS may contribute to the preservation of normal lung capacity to clear edema fluid.

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Mechanical ventilation

Most patients with ARDS require mechanical ventilation. Ventilator-induced lung injury (VILI) is the acute lung injury inflicted by biochemical stress due to mechanical ventilation. VILI contribute to the morbidity and mortality of patients with ARDS (Slutsky and Ranieri, 2013). Clinically relevant rat model of ventilator-induced lung injury demonstrated that high tidal volume of 40ml/kg and elevated airway pressures of 35 cmH2O by mechanical ventilation rapidly impair alveolar epithelial injury and reduce AFC in the lung by decreasing in Na/K-ATPase activity, inducing cell death, inflammation, and disrupting cell junctions (Lecuona et al., 1999; Frank et al., 2002; Frank et al., 2003b). Since alveolar edema fluid can inactivate surfactant and reduces functional lung volume, the impairment of AFC is an important mechanism of VILI. The success of lung protective ventilation in reducing mortality in patients with ARDS is potentially attributed in part to the preservation or restoration of AFC in the injured lung.

REGULATION AND TREATMENT FOR ALVEOLAR FLUID CLEARANCE

β-adrenergic agonist

β-adrenergic stimulation markedly increases AFC by stimulation of active sodium transport across the alveolar epithelium in the sheep, dogs, rats, mice and the ex vivo human lung (Crandall et al., 1986; Berthiaume et al., 1987; Berthiaume et al., 1988; Sakuma et al., 1994; Sakuma et al., 1997; Sartori et al., 2002b). In addition, the release of endogenous catecholamines associated with septic shock stimulates AFC by a β-adrenergic stimulation of active sodium transport, providing the evidence for a mechanism that can protect against alveolar edema in pathological conditions such as sepsis (Pittet et al., 1994). Furthermore, experimental studies demonstrated that AFC impaired by hypoxia, infection, or VILI is reversed rapidly by β-adrenergic agonist, suggesting a therapeutic potential for β-adrenergic agonist to treat acute lung injury (Vivona et al., 2001; Frank et al., 2003b; Wolk et al., 2008). Clinical trials indicated prophylactic inhalation of a β-adrenergic agonist reduces the risk of high-altitude pulmonary edema (Sartori et al., 2002a) and aerosolized salbutamol accelerates the resolution of lung edema and improves blood oxygenation after lung resection (Licker et al., 2008). However, recent phase 3 clinical trials failed to show beneficial effects of inhaled or intravenous β-adrenergic agonist on ARDS, in which β-adrenergic agonist increased the rate of supraventricular tachycardia and possibly mortality (Perkins et al., 2006; Matthay et al., 2011; Gao Smith et al., 2012). Taken together, these data suggest that either inhaled or intravenous β-adrenergic therapy to reduce the lung edema is not beneficial for patients with ARDS in clinical settings. Plausible explanation for why β-adrenergic therapy did not improve outcome is that the injured alveolar epithelium may have been unable to respond to a β-adrenergic agonist. Several preclinical studies demonstrate that β-adrenergic agonists can reduce pulmonary edema in the early phase of lung injury, but in patients with ARDS the epithelium is widely injured with apoptosis and necrosis, and therefore may lose the ability to respond to β-adrenergic agonist.

Anti-inflammatory therapies

Since proinflammatory cytokines increase permeability and impair AFC, anti-inflammatory drugs such as steroids may help preserve AFC. Glucocorticoids modulate the dysregulated

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immune system and sometimes are prescribed as an adjunctive treatment for ARDS (Horby et al., 2021). Recent clinical trials have demonstrated a beneficial effect of glucocorticoids in COVID-19 ARDS and potentially in non-COVID ARDS (Villar et al., 2020; Horby et al., 2021). The potential benefit of glucocorticoids is explained in part by the ability of glucocorticoids to upregulate AFC. Multiple experimental studies demonstrated that dexamethasone, a long-acting potent glucocorticoids is capable of modulating ENaC and Na/K-ATPase by transcriptional, translational, and posttranslational mechanisms and increase AFC, thereby accelerating recovery from pulmonary edema (Barquin et al., 1997; Dagenais et al., 2001; Noda et al., 2003) . Furthermore, dexamethasone prevents inhibition of AFC due to hypoxia by stimulating mRNA expression of Na/K-ATPase and ENaC (Guney et al., 2007).

Although TNF-α is a potential pro-inflammatory cytokine, lectin-like domain of TNF-α have protective effects on lung function in ARDS. Whereas TNF-α signaling cause inflammation and increase permeability, the TNF-α lectin-like domain directly activated ENaC and increased AFC (Fukuda et al., 2001; Elia et al., 2003; Lucas et al., 2021). Application of TIP peptides that mimic this lectin-like domain enhances AFC by stimulating ENaC and also reduces alveolar permeability, which prevents further edema formation in experimental lung injury model (Hartmann et al., 2014). Taken together, administration of TNF-α lectin-like domain is a potential therapy to attenuate pulmonary edema in ARDS.

Mesenchymal stromal cells

Mesenchymal stromal cells (MSCs) are multi-potent cells isolated from bone marrow, umbilical cord, and fat tissue that can differentiate into a variety of cells, have potent immunomodulatory effects, and secrete paracrine factors that can enhance endothelial and epithelial repair (Charbord, 2010; Ghannam et al., 2010; Parekkadan and Milwid, 2010; Lee et al., 2011). In experimental models of sepsis, tracheal instillation of MSCs ameliorated *E. coli* induced lung injury and reduced bacterial burden in the lung, possibly by enhancing macrophage phagocytosis and increasing alveolar antimicrobial peptide concentration (Mei et al., 2010; Devaney et al., 2015). Treatment with MSCs reduced pulmonary edema and improved survival in *E. coli* endotoxin-induced lung injury in mice, rat, and sheep (Gupta et al., 2012; Asmussen et al., 2014; Devaney et al., 2015). In *ex-vivo* human lungs injured with live *E. coli*, MSCs preserved AFC, reduced inflammation, and increased bacterial clearance, in part by keratinocyte growth factor secretion (Lee et al., 2009; Lee et al., 2013). This protective effect has been explained by the ability of keratinocyte growth factor to upregulate expression of Na/K-ATPase, stimulate the proliferation of alveolar type II cells, and enhance macrophage phagocytosis (Guery et al., 1997; Wang et al., 1999; Portnoy et al., 2004). In older mice, the release of soluble mediators from influenza A H5N1 virus-infected alveolar epithelial cells impair AFC due to down-regulation of ENaC and CFTR. This pathology was reduced by MSCs treatment (Chan et al., 2016). However, in young mice (6-8 weeks of age), influenza-caused disruption of the alveolar-capillary barrier is unresponsive to MSCs (Gotts et al., 2014), suggesting that MSCs treatment may be beneficial for patients with severe lung injury caused by influenza viruses such as H5N1, especially elderly patients. Other studies indicate that therapeutic effects of MSCs may also attribute to mitochondorial transfer, or the release of microvesicles (Islam et al., 2012; Abraham and Krasnodembskaya,

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2020). Taken together, these preclinical studies suggest that MSCs have beneficial effects on ARDS by a variety of mechanisms, and indicate that immunomodulatory cell therapy may be an effective adjunctive treatment to improve outcomes in patients with ARDS (Walter et al., 2014; Matthay, 2015). Based on these preclinical data, phase 1 and 2 clinical trials have been done and demonstrated that intravenous administration of MSCs is safe in patients with ARDS (Wilson et al., 2015; Matthay et al., 2019a). Post-hoc analysis of this phase 2 trial found that MSCs reduced biological evidence of lung injury in patients with ARDS (Wick et al., 2021a). Larger trials to assess the efficacy and the viability of MSCs as a therapy for ARDS are currently ongoing (NCT03818854). Figure 3 summarizes the clinically relevant mechanisms that enhance AFC.

FUTURE RESEARCH

Multiple pharmacotherapies for ARDS have been tested in clinical trials, however, none have shown efficacy to date, including β adrenergic agonist and keratinocyte growth factor (Perkins et al., 2006; Matthay et al., 2011; Gao Smith et al., 2012; McAuley et al., 2017). Translating insights from experimental studies into effective therapies for human ARDS has been challenging except for supportive care therapies such as lung protective ventilation and prone positioning (Guérin et al., 2013). Indeed, the search for specific pharmacotherapies that effectively enhance AFC has failed, despite decades of promising preclinical research (Matthay et al., 2019b). Conceivably, testing of therapies at an early phase of clinical acute lung injury may be more effective (Wick et al., 2021b).

Recently, analyses of clinical data and biological samples from large clinical trials have enabled studies focused on heterogeneity in ARDS, specifically on the identification of sub-phenotypes of ARDS that have differential response to therapies (Calfee et al., 2014). In ARDS, clinical and biological heterogeneity has long been suspected as a potential barrier to successful development of therapeutics. Recent analysis of combined clinical and biological data in five clinical cohorts identified two sub-phenotypes of ARDS, termed hyper-inflammatory and hypo-inflammatory ARDS (Calfee et al., 2014). Patients with hyper-inflammatory sub-phenotypes are characterized by increased inflammatory signals, as evidenced by high plasma levels of IL-6, IL-8, and sTNFR-1. These phenotypes have widely divergent clinical outcomes and respond differentially to therapies such as simvastatin, fluid therapy, and mechanical ventilation (Sinha and Calfee, 2019). It is possible that pharmacotherapies that effectively enhance AFC improve clinical outcomes in patients with hyper-inflammatory sub-phenotype, since inflammation impair the alveolar epithelium and decrease AFC. Thus, pharmacologic therapies focused on treatment responsive subphenotypes of ARDS may be helpful (Wick et al., 2022).

A major barrier to improved outcomes from ARDS is the lack of functional alveolar epithelium in ARDS, probably due to necrosis and apoptosis of epithelial cells (Ware and Matthay, 2000). Supporting this hypothesis, meta-analysis of recent clinical trials indicates plasma soluble receptor for advanced glycation end-products level (sRAGE), a biomarker of epithelial injury, is an independent predictor of 90-day mortality in ARDS (Jabaudon et al., 2018). Thus, it is necessary to understand the mechanisms of epithelial cell death and regeneration. Some pre-clinical studies demonstrated the potential efficacy of progenitor

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cells for the treatment of COVID-19 ARDS (Chen et al., 2020; Lanzoni et al., 2021). Further studies are needed to promote the repair of epithelium including enhancing tight barrier function, surfactant secretion, and AFC.

There is new evidence that the damage to alveolar epithelial glycocalyx, a thin layer existing on the epithelial cells induces surfactant dysfunction and contributes to the lung injury in ARDS (Rizzo et al., 2022). In addition, some recent experimental studies suggest that two-pore-domain potassium channels, which are generally known for their unusual gating properties leading to so-called “leak homeostasis” that stabilize the resting plasma membrane potential, are involved in alveolar cell proliferation, cytokine secretion, and surfactant protein production (Schwingshackl et al., 2012; Schwingshackl et al., 2017). In a mouse study, activation of the two-pore-domain potassium channel protects against hypoxia and influenza-induced lung injury (Zyrianova et al., 2020; Zyrianova et al., 2022). These new insights of alveolar epithelial function might represent a novel therapeutic approach for ARDS.

Beyond the experimental proof, most recent clinical trials for COVID-19 have focused on new targets or repurposing of existing drugs to treat ARDS, such as dexamethasone (Horby et al., 2021), anti-cytokine therapy (Matthay and Luetkemeyer, 2021; Rosas et al., 2021), and heparin (Lawler et al., 2021). Future experiments are required to investigate the detailed mechanisms and influence of these and other therapies on alveolar epithelial cell function and repair, including AFC.

CONCLUSIONS

In this review, we have provided a commentary of AFC in the normal lung, the mechanisms of impaired AFC, and then outlined the regulation of AFC. Finally, we have summarized ongoing challenges and possible future research that may offer a promising therapy for ARDS. Over the past several decades, multiple experimental studies have been done to identify the mechanisms and the regulation of AFC. However, to date, promising therapies in preclinical settings have failed to achieve effective treatment for patients with ARDS. However, new approaches are being evaluated, including testing therapies in sub-phenotypes of ARDS and delivering therapies at an earlier phase of ARDS, when patients are receiving high-flow nasal oxygen (Matthay et al., 2021).

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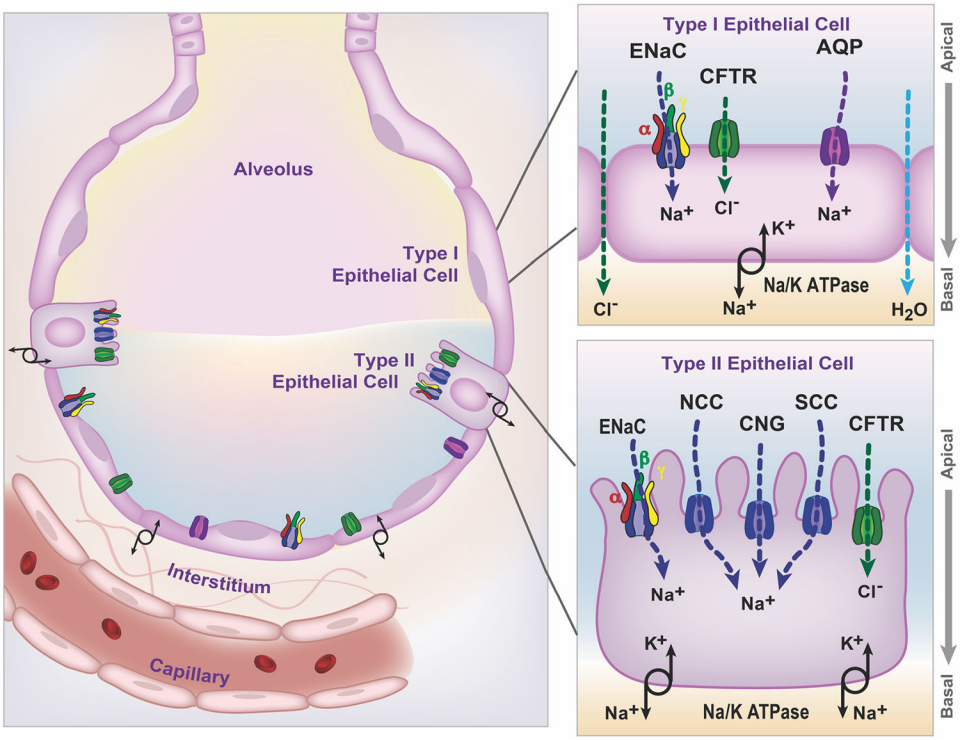

Figure 1. Normal alveolar fluid clearance pathways.

The interstitial, capillary, and alveolar compartments are shown with pulmonary edema fluid in the alveolus. Both type I and type II alveolar epithelial cells are involved in transepithelial ion transport. Sodium (Na^+) is transported across the apical side of the epithelial cells through the epithelial sodium channel (ENaC) and other apical sodium channels, including nonselective cation channels (NCC), cyclic nucleotide-gated channels (CNG), and other selective cation channels (SCC), and then across the basolateral side via the sodium/potassium ATPase (Na/K-ATPase). Chloride (Cl^-) is transported by transcellular route through the cystic fibrosis transmembrane conductance regulator (CFTR) or by a paracellular route. This vectorial ion transport creates an osmotic gradient that drives the clearance of alveolar edema fluid. Water (H_2O) is crossing by transcellular route through an aquaporin 5 (AQP5) channel or by a paracellular route. Figure prepared by Diana Lim.

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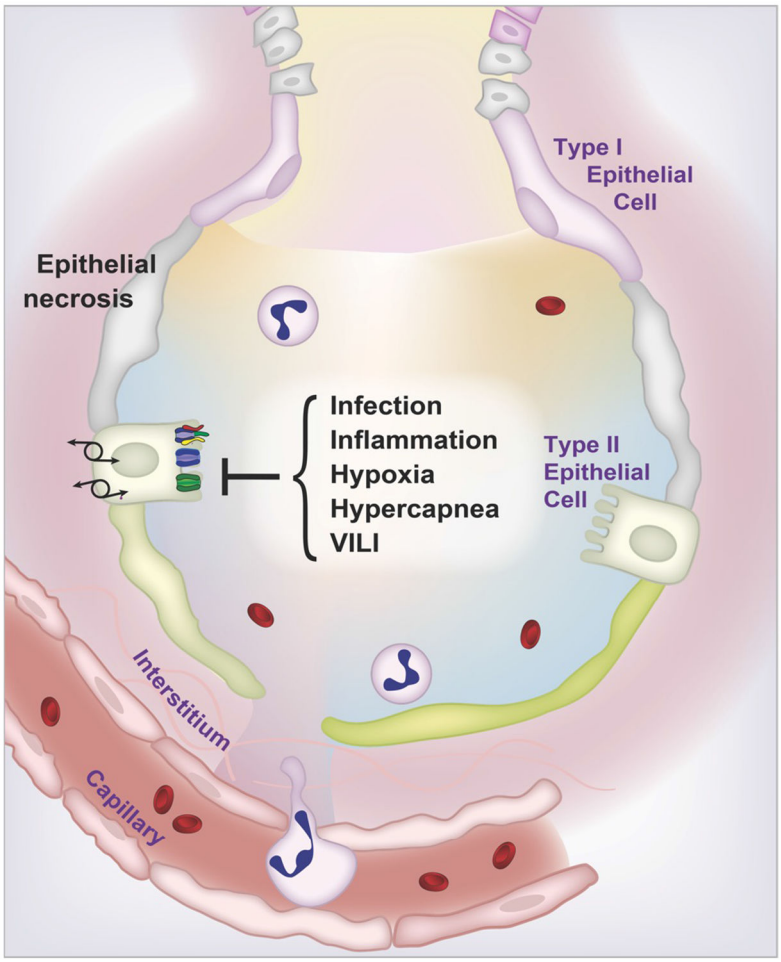

Figure 2. Impaired alveolar fluid clearance pathways.

Shown are some of the clinically relevant factors that cause impaired alveolar fluid clearance in acute lung injury. These factors have been investigated in experimental and clinical studies. Type I and type II alveolar epithelial cell necrosis is shown, which is an important mechanism for alveolar fluid accumulation due to the loss of epithelial barrier function and the ability to generate alveolar fluid clearance. Neutrophils have an important role in host defense but can cause alveolar damage and prevent the upregulation of alveolar fluid clearance by catecholamines. The other factors shown are discussed in text. Figure prepared by Diana Lim.

Abbreviations: VILI, ventilator induced lung injury

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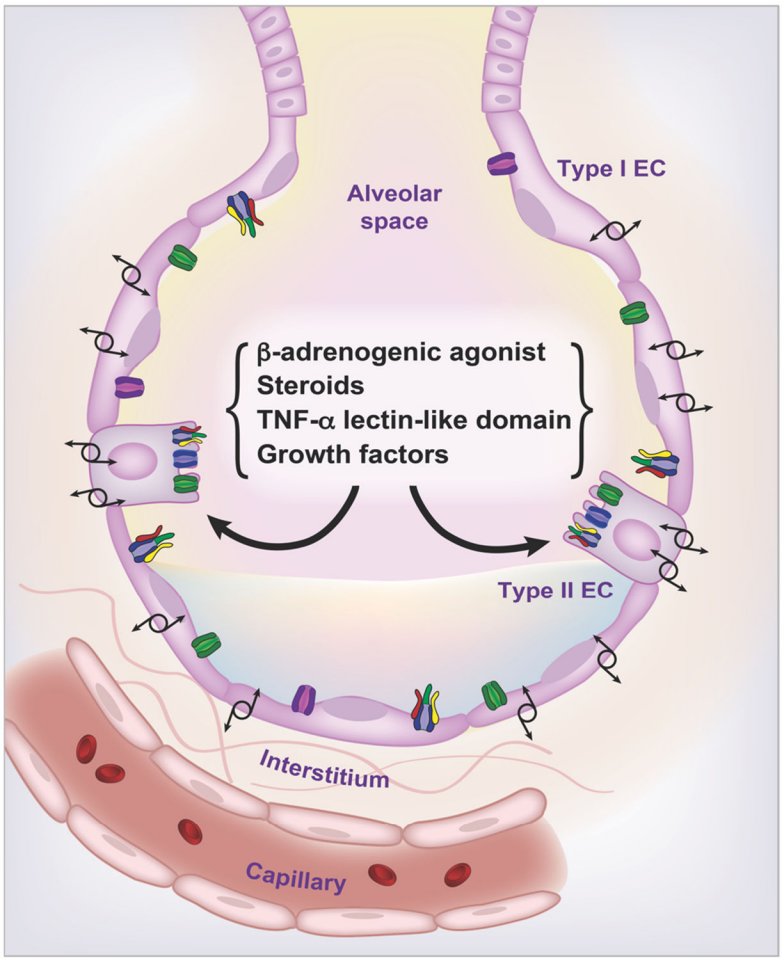

Figure 3. Up-regulated alveolar fluid clearance pathways

Shown are some of the clinically relevant mechanisms that can enhance alveolar fluid clearance. These mechanisms have been investigated in experimental and clinical studies. Mechanisms for increased clearance include β adrenergic agonist, steroids, growth factors, and TNF-α lectin like domain. Figure prepared by Diana Lim.